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Abstract.

Introduction: Pulmonary sarcoidosis is considered refractory if glucocorticoids (GCs) at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and methotrexate (MTX), including their combined use, are not effective enough to achieve clinical remission.

Aim: To study the rate of refractory pulmonary sarcoidosis after conventional treatment with methylprednisolone (MP) and/or MTX in patients with newly diagnosed disease.

Materials and Methods: 250 patients with newly diagnosed pulmonary sarcoidosis (106 men and 144 women; mean age 44 years) were examined. Radiological stage II was established in 237 (94.8%) patients, stage III — in 13 (5.2%). GCs therapy was carried out using MP in 190 patients at an initial dose of 0.4 mg/kg/day for 4 weeks with a gradual decrease to a maintenance dose (0.1 mg/kg/day) by the end of the 6th month. In the presence of contraindications or serious adverse effects of MP (60 patients), MTX was used at a dose of 15 mg/week. Patients without contraindications and serious adverse effects of MP treated with MTX, in case of initial therapy failure, were prescribed combined therapy with MP (12 mg/day) and MTX (10 mg/week).

Results: Based on combination therapy outcomes, as well as taking into account the cases of MTX therapy failure in patients with contraindications or serious adverse effects of GCs therapy, refractory pulmonary sarcoidosis was diagnosed in 27 (10.8%) patients. Patients with refractory pulmonary sarcoidosis were more likely to have stage III disease (Pearson's χ² test = 5.766, p = 0.031), as well as extrapulmonary lesions (χ² test = 4.672, p = 0.031).

Conclusion: The high rate of conventional therapy failure using first- and second-line medications in patients with newly diagnosed sarcoidosis determines the relevance of further study of the causes, development of risk criteria and new approaches to the treatment of refractory pulmonary sarcoidosis.

Key words. Refractory pulmonary sarcoidosis, incidence, methylprednisolone, methotrexate.

Introduction.

Sarcoidosis is a multisystem disorder of unknown cause(s). It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The diagnosis is established when clinical and radiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas [1,2]. In 2021, the ERS Task force report “ERS clinic practice guidelines on treatment of sarcoidosis” was published, which identified completely new approaches to the treatment of patients with sarcoidosis [3]. The main principle of treatment of patients with pulmonary sarcoidosis is to achieve a balance between: a) minimizing the risk of disability, death due to lung damage or reduced quality of life; and b) the risk of comorbidity and a decrease in the quality of life as a result of the effects of GCs and other types of therapy [3].

According to the European Respiratory Society (ERS) 2021 guidelines, GCs remain the first-line therapy for patients with pulmonary sarcoidosis. In the treatment of pulmonary sarcoidosis without an involvement of heart, central nervous system (CNS), and eyes, GCs are used in medium doses (the initial dose is usually 0.5 mg/kg of body weight per day, prednisolone equivalent, for at least 4 weeks). The dose is then tapered within 8 weeks so that by the end of the third month it is 0.25 mg/kg. After 3 months from the start of treatment, its efficacy is assessed. If clinical and radiological condition improved, the dose should gradually be tapered to 0.125 mg/kg by the end of the 6th month. During the subsequent period of treatment, the dose remains unchanged [4].

However, some patients may have contraindications to GCs. In addition, GCs therapy may be not effective or lead to the development of serious adverse effects. In such cases, treatment with a second-line drug MTX is recommended. If GCs and MTX failed, treatment with the third-line drug infliximab should be suggested [3].

About 5% of patients with sarcoidosis die of this disease [3,5,6]. Pulmonary and cardiac complications are the most common causes of death from sarcoidosis in its chronic course, which in turn is due to refractoriness.

There is no generally accepted definition of refractory sarcoidosis, and there are no recommendations for its treatment.

In 2016, Korsten et al. proposed the following definition for refractory pulmonary sarcoidosis:

1. Progressive pulmonary disease despite GCs therapy at adequate dosage defined as at least 10 mg of prednisone once a day and duration of therapy of at least 3 months after initial dosages of 20–40 mg per day for 1–3 months and need for additional therapy due to lack of efficacy, GCs toxicity or severe side effects

2. Treatment started for impaired quality of life due to progressive pulmonary symptoms with or without additional disease manifestations (e.g., disfiguring disease, neurosarcoidosis, etc.) [7].

Thus, this definition of refractory sarcoidosis is limited only to refractoriness to GCs therapy without considering the potential effect of alternative (MTX) treatment. Goldman and Judson proposed to use the term “Corticosteroid refractory sarcoidosis” to characterize this disease state [8].

In the STAT cohort (sarcoidosis treated with tumour necrosis factor antagonists), refractory sarcoidosis was defined as a
condition in which second-line immunosuppressants were not sufficient to achieve satisfactory control of the disease [9]. In a prospective trial, Sweiss et al. defined refractory pulmonary sarcoidosis as the disease in patients with symptomatic sarcoidosis taking GCs over 10 mg/day or symptomatic sarcoidosis with a GCs sparing agent [10].

El Jammal et al suggested to define refractory sarcoidosis as a situation in which GCs and second-line treatment(s) (MTX, azathioprine, leflunomide, antimalarials, or mycophenolate mofetil) are not sufficient to achieve clinical remission with a GCs dosage under 10 mg/day [11].

Considering the 2021 ERS recommendations providing for MTX only as a second-line drug, and considering the need for a combination treatment in cases of monotherapy failure, the definition by El Jammal et al. can be formulated as follows:

Pulmonary sarcoidosis should be considered refractory if GCs at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and MTX, including their combined use, are not effective enough to achieve clinical remission.

Below are the main options of therapy failure, to be considered refractory pulmonary sarcoidosis.

1. Insufficient efficacy of MTX monotherapy prescribed as a starting agent due to contraindications to GCs, or due to serious adverse effects of GCs.
2. Insufficient effectiveness of combination therapy using GC and MTX, prescribed due to resistance to GCs.

Data on the incidence of refractory sarcoidosis are highly variable, ranging from 10% to 20–40% of patients after GCs treatment, including GCs sparing agents [7,12].

Aim.
The aim was to study the rate of refractory pulmonary sarcoidosis after treatment with MP and/or MTX in patients with newly diagnosed disease. Materials and Methods.

250 patients with pulmonary sarcoidosis (general group) were examined, including 106 men (42.4 %) and 144 women (57.6 %), mean age 44 years (22–74). Radiological stage II was established in 237 (94.8 %) patients, stage III – in 13 (5.2 %).

In accordance with an official document of American Thoracic Society (ATS) “Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline” [13], the diagnosis of sarcoidosis was based on three main criteria: compatible clinical manifestations, the presence of non-necrotizing granulomatous inflammation in one or more tissue samples (if a lung biopsy was necessary), and the exclusion of alternative causes of granulomatous process.

All patients were examined by high-resolution computed tomography (CT) using an Aquilion TSX-101A multislice CT scanner (Toshiba). CT results were evaluated using the criteria described by Veltkamp and Grutters [14].

The main criterion for inclusion of patients in the study was the diagnosis of newly diagnosed pulmonary sarcoidosis without any prior specific therapy. The second important inclusion criterion was the absence of CT signs of interstitial lung fibrosis, which allows to exclude patients with a long-term disease with the maximum probability.

<table>
<thead>
<tr>
<th>Table 1. Extrapulmonary manifestations of sarcoidosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary lesions</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Peripheral lymph nodes</td>
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<tr>
<td>Joints</td>
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<tr>
<td>Heart</td>
</tr>
<tr>
<td>Bones</td>
</tr>
<tr>
<td>CNS</td>
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<tr>
<td>Eyes</td>
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<tr>
<td>In total</td>
</tr>
</tbody>
</table>

Extrapulmonary manifestations of sarcoidosis were observed in 14.8 % of patients (Table 1). At the same time, skin lesions were more often observed (6.8 %).

Treatment of patients with pulmonary sarcoidosis was prescribed according to the recommendations of the Regulations of the ATS, ERS and the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) "Statement on Sarcoidosis", 1999 [2] and the national clinical protocol "Sarcoidosis" (2014). Patients with newly diagnosed pulmonary sarcoidosis are prescribed first-line medications (GCs) in the following cases:

• At all stages of sarcoidosis with extrapulmonary manifestations – sarcoidosis of heart, CNS, eyes.
• At stage II sarcoidosis with clinical manifestations (cough, shortness of breath, chest pain, decreased physical activity) and/ or with moderate lung function impairment.
• Progression of the disease according to CT data (enlargement of lymph nodes, increase in areas of parenchymal lesions) after a 3-month follow-up period after spontaneous remission.
• At stage III of the disease, spontaneous remissions are relatively rare in this category of patients. In addition, most patients with stage III sarcoidosis have pronounced clinical manifestations (shortness of breath, cough), impaired ventilation and diffusing capacity of the lungs.

It should be noted that the above indications for GC therapy are in compliance with ERS 2021 recommendations [3]. GCs therapy using MP was initiated in 190 patients (Group 1 - MP). The initial MP dose was 0.4 mg/kg daily for 4 weeks, and then the dose was gradually reduced to 0.2 mg/kg by the end of the 3rd month and to 0.1 mg/kg (maintenance dose) by the end of the 6th month. After the achievement of clinical cure phase, MP therapy at a dose of 0.1 mg/kg/day continued for at least 6 months. Since in the majority of patients the normalization of the clinical condition and CT data usually occurs at the 3rd visit (after 6 months of treatment), the total duration of GCs therapy was at least one year on average.

Based on the data of numerous studies on the efficacy and safety of MTX in patients with pulmonary sarcoidosis, including large retrospective studies, MTX was prescribed in the presence of contraindications to GCs therapy [3,15-18]. The following contraindications for GCs use were established: diabetes mellitus, osteoporosis, severe arterial hypertension, peptic ulcer of the stomach and duodenum, thrombophlebitis, mental diseases. MTX as monotherapy was also prescribed in cases of serious adverse effects of GCs (uncontrolled hyperglycemia,
mental disorders, osteoporosis). Eighteen patients with newly diagnosed pulmonary sarcoidosis had a negative attitude towards long-term systemic hormonal therapy, and therefore preferred the alternative treatment with MTX. In total, MTX monotherapy was used in 60 patients (Group 2 - MTX).

MTX was prescribed at a dose of 15 mg once a week. Before starting therapy and monthly during treatment, a complete blood count and blood chemistry were performed to determine the concentration of ALT, creatinine, leukocytes, and platelets.

Treatment outcomes were assessed on the basis of clinical examination and CT scans at 3, 6, and 12 months of therapy and until clinical cure was achieved. With the disease progression or the absence of a positive effect of GCs (improvement) after 6 months of treatment, patients were prescribed combination therapy: MP at a dose of 12 mg/day daily and MTX at a dose of 10 mg weekly. A group of patients without contraindications and serious adverse effects of MP who received MTX, with initial therapy failure, was also prescribed combination therapy.

In patients with progression or stabilization of the disease, despite the combined therapy for 6 months, the course of pulmonary sarcoidosis was assessed as refractory. In addition, a few cases of MTX monotherapy failure in patients with contraindications or serious adverse effects of GCs were considered refractory sarcoidosis.

**Statistical methods.**

Pearson's χ² test was used to compare data on categorical variables presented as numbers and percentages. All measurements were two-sided with a significance level of p < 0.05.

**Results.**

Analysis of treatment outcomes in patients with newly diagnosed pulmonary sarcoidosis showed that the therapy was effective in 188 (75.2 %) patients. At the same time, treatment with MTX did not significantly differ from GCs therapy with MP in terms of the success rate (Table 2).

Resistence to GCs therapy (progression or stabilization during treatment) was observed in 55 (28.9%) patients. MTX therapy failure was observed significantly less frequently (7 patients - 11.7%; χ² test = 7.300; p = 0.007), predominantly in patients with macronodular lesions of the parenchyma.

Combination therapy with MP and MTX was prescribed due to the insufficient efficacy of GCs therapy, and in patients from the MTX group who had no contraindications or serious adverse effects of GCs requiring the MP discontinuation.

Based on the outcomes of combination therapy, as well as considering cases of MTX failure in patients with contraindications or serious adverse effects of GCs therapy, refractory pulmonary sarcoidosis was diagnosed in 27 (10.8%) patients.

Table 3 shows the characteristics of patients with refractory pulmonary sarcoidosis.

As it can be seen from the table, women prevailed (66.7 %) among patients with refractory pulmonary sarcoidosis, the average age was 46 years (25–74), same as in general group. Patients with refractory pulmonary sarcoidosis were significantly more likely to have stage III disease, as well as extrapulmonary lesions.

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Successful therapy n = 223</th>
<th>Refractory sarcoidosis n = 27</th>
<th>χ² test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>44 (22–74)</td>
<td>46 (25–74)</td>
<td>n/a</td>
</tr>
<tr>
<td>Males</td>
<td>97 (43.5 %)</td>
<td>9 (33.3 %)</td>
<td>1.019 p=0.313</td>
</tr>
<tr>
<td>Females</td>
<td>126 (56.5 %)</td>
<td>18 (66.7 %)</td>
<td>1.019 p=0.313</td>
</tr>
<tr>
<td>Radiological stage II</td>
<td>214 (96 %)</td>
<td>23 (85.2 %)</td>
<td>5.766 p=0.018*</td>
</tr>
<tr>
<td>Radiological stage III</td>
<td>9 (4 %)</td>
<td>4 (14.8 %)</td>
<td>5.766 p=0.018*</td>
</tr>
<tr>
<td>Extrapulmonary lesions</td>
<td>25 (11.2 %)</td>
<td>7 (25.9 %)</td>
<td>4.672 p=0.031*</td>
</tr>
<tr>
<td>Including: skin</td>
<td>15 (6.7 %)</td>
<td>2 (7.4 %)</td>
<td>0.018 p=0.895</td>
</tr>
<tr>
<td>liver</td>
<td>4 (1.8 %)</td>
<td>1 (3.7 %)</td>
<td>0.448 p=0.504</td>
</tr>
<tr>
<td>joints</td>
<td>2 (0.9 %)</td>
<td>1 (3.7 %)</td>
<td>1.600 p=0.206</td>
</tr>
<tr>
<td>heart</td>
<td>2 (0.9 %)</td>
<td>1 (3.7 %)</td>
<td>1.600 p=0.206</td>
</tr>
<tr>
<td>bones</td>
<td>2 (0.9 %)</td>
<td>1 (3.7 %)</td>
<td>1.600 p=0.206</td>
</tr>
<tr>
<td>CNS</td>
<td>0</td>
<td>1 (3.7 %)</td>
<td>8.292 p=0.004*</td>
</tr>
</tbody>
</table>

**Discussion.**

Most investigators consider pulmonary sarcoidosis to be refractory when first-line medicinal products (GCs) at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and second-line medicinal products (MTX), including their combined use, are not effective enough to achieve clinical remission [9,10,11].

Goldman and Judson proposed considering all cases of disease progression at the stage of tapering the dose of GCs from initial to the maintenance one (at least 10 mg/day prednisolone equivalent) “corticosteroid refractory sarcoidosis” [8].

Significant variability in the incidence of refractory sarcoidosis seems to be due to the lack of generally accepted criteria for the diagnosis, as well as the inclusion of patients with a different course of sarcoidosis, from newly diagnosed to chronic with a long history of the disease, in the study.

The main inclusion criterion in our study was the diagnosis of newly diagnosed sarcoidosis without previous specific therapy, as well as the absence of CT signs of interstitial pulmonary
fibrosis in order to exclude patients with a long history of the disease.

Even though the criteria for the diagnosis of sarcoidosis and the methods of treatment corresponded to international standards, refractory sarcoidosis after treatment with MP and/or MTX was observed in a significant proportion of cases - in 10.8 % of patients [2,3,13].

Conclusion.

The high rate of conventional therapy failure in patients with newly diagnosed pulmonary sarcoidosis using first- and second-line medications determines the relevance of further study of the causes, development of risk criteria and new approaches to the treatment of refractory pulmonary sarcoidosis.

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Conflict of interest.

The authors declare that they have no conflict of interest.

REFERENCES


Цель: изучить частоту рефрактерного саркоидоза легких после стандартного лечения метилпреднизолоном (МП) и/или МТХ у пациентов с впервые диагностированным заболеванием. Материалы и Методы: Обследовано 250 больных впервые диагностированным саркоидозом легких (106 мужчин и 144 женщины; средний возраст – 44 года. II рентгенологическая стадия была установлена у 237 (94,8 %) больных, III – у 13 (5,2 %). GC-терапия проводилась с использованием МП у 190 больных в начальной дозе 0,4 мг/кг/день в течение 4-х недель с постепенным ее снижением до поддерживающей (0,1 мг/кг/день) к концу 6-го месяца. При наличии противопоказаний или серьезных побочных эффектов МП (60 пациентов), применяли МТХ в дозе 15 мг/ нед. Пациентам без противопоказаний и серьезных побочных эффектов МП, получавших МТХ, при неэффективности инициальной терапии назначали комбинированную терапию МП (12 мг/день) и МТХ (10 мг/нед). Результаты: По результатам комбинированной терапии, а также с учетом случаев неуспешной МТХ терапии у пациентов с противопоказаниями или серьезными побочными эффектами GC терапии, рефрактерный саркоидоз легких был констатирован у 27 (10,8 %) пациентов. У больных с рефрактерным саркоидозом легких чаще отмечалась III стадия заболевания (критерий χ2 Пирсона = 5,766, р =
0,018), а также экстрапульмональные поражения (критерий \( \chi^2 = 4,672, p = 0,031 \)).

Заключение: Высокая частота случаев неуспешной стандартной терапии препаратами первой и второй линии у пациентов с впервые диагностированным саркоидозом обусловливает актуальность дальнейшего изучения причин, разработки критериев риска и новых подходов к лечению рефрактерного саркоидоза легких.

Ключевые слова: Refractory pulmonary sarcoidosis, incidence, methylprednisolone, methotrexate.